REMARKS

Claims 1-15 were previously canceled by preliminary amendment. Applicants have now canceled claims 40, 42, 43, and 45-47 without prejudice, and have amended Claims 16, 17, 21-25, 29-36, 38, 39, 41, and 44. New Claims 48-51 have been added.

The method claims have been amended to recite an additional step of "recovering a solution of the at least one blood clotting protein", and various dependent method claims now recite a "blood clotting protein isolated from the recovered solution". This step is believed to be supported by the specification, *e.g.*, at pages 7-8, the first full paragraph at page 9, and Table 1 at page 14. In particular, Table 1 states that the claimed method (*e.g.*, Gradiflow™) does not include a "co-precipitation" step. In other words, the present specification describes a process in which the blood clotting protein is recovered from the claimed process as substantially *dissolved* fibrinogen, rather than as a precipitate. The specification also describes additional process steps for isolating a blood clotting protein from the recovered solution (*e.g.*, by ultrafiltration at page 9, lines 7-11), further indicating that the blood clotting protein is isolated from a recovered solution of blood clotting protein. Moreover, Table 1 and page 1, lines 23-28 of the specification describe the improved properties of blood clotting proteins prepared by the claimed process, compared to precipitation methods.

Minor amendments to the claims were also made to improve the clarity of the claim language (*e.g.*, adding the expression "the steps of" to claim 16).

In addition, new claims 48-53 have been added. These claims are believed to be supported by claims 16, 22, 24, and 32, and in the specification at pages 7-14.

Claims 16-39, 41, 44, and 48-51 are active. Applicants believe that no new matter would be added by entry of these amendments and new claims 48-51.

Objection to Claims 45-47

Claims 45-47 have been objected to as being "substantial duplicate[s] of claim 44". In the interest of advancing prosecution of the claims, Applicants have obviated the objection by canceling claims 45-47 without prejudice to their further prosecution. Accordingly, Applicants respectfully request that the objection be withdrawn.

Obviousness-Type Double Patenting Rejection of Claims 16-47

The rejection of claims 16-47 under the judicially created doctrine of obviousness-type double patenting is obviated by the filing herewith of a Terminal Disclaimer over U.S. 6,402,913. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejection of Claims 16-47 under 35 U.S.C.§ 103(a)

Applicants respectfully traverse the rejection of the claims as obvious over the combination of Laustsen (U.S. 5,437,774), Gritzner (U.S. 4,043,895) and Margolis (U.S. 5,650,055). The combination of Laustsen, Gritzner, and Margolis fails to support a *prima facie* case of obviousness because the combination "fails to teach or suggest all the claim limitations", and the claimed invention reasonably provides significant improvements over the precipitation process taught by the combination of Laustsen, Gritzner, and Margolis.

The Examiner states that Laustsen "fails to describe the use of electrophoretic separation of the blood clotting proteins, such as fibrinogen", and cites col. 9, lines 1-9 of Gritzner "to show the use of electrophoresis to separate fibrinogen from other proteins". Margolis is silent in regard to the isolation of blood clotting proteins.

However, col. 9, lines 1-9 of Gritzner states that "protein precipitation (generally fibrinogen) takes place outside the cell on the holding of the output A stream" (emphasis added). That is, Gritzner describes an electrophoretic process producing a precipitated protein rather than the *dissolved* blood clotting protein recovered in the claimed method (*e.g.*, step (e) of claim 16). Thus, the combination of Laustsen and Gritzner fails to support a *prima facie* case of obviousness because it "fails to teach or suggest all the claim limitations" (MPEP §§ 2142 and 2143.03). Accordingly, Applicants respectfully request that the rejection be withdrawn.

Moreover, as discussed at page 1, lines 23-28 of the present specification, fibrinogen isolated by conventional precipitation methods has inferior properties and is prepared in inferior yield compared to fibrinogen prepared by the claimed method in which *dissolved* blood clotting protein (*e.g.*, fibrinogen) is recovered in substantially higher yield and purity, and with significantly improved clotting properties (*see* discussion in the present specification at page 1, lines 23-28 and pages 14-16). Reasonably, the claimed methods, systems, and isolated fibrinogen would also be expected to have superior properties

compared to the methods, systems, and fibrinogen taught by the combination of Laustsen and Gritzner, since this combination teaches a precipitation method for isolating fibrinogen. Thus, the combination of Laustsen and Gritzner cannot reasonably suggest the claimed invention (MPEP § 2141). Accordingly, Applicants respectfully request that the rejection be withdrawn.

New claims 48-50 are also not suggested by the combination of Laustsen, Gritzner, and Margolis.

Laustsen describes selective membranes having a pore size "greater than 1 kD and up to a 2 μm pore size" (col. 4, lines 2-3), "usually being in the range from 600 D to 1,000 kD, preferably being above 10 kD" (col. 7, lines 27-30) and exemplifies a process for separating bovine hemoglobin from bovine serum albumin in which the sample pH is 6.0 or 6.3, and the dialysate pH is 5.3 (col. 11, lines 19-26). Thus, Laustsen fails to describe the claimed isolation of fibrinogen from blood plasma by a method combining a first selective membrane having a molecular mass cut off of about 300 kDa, a second selective membrane (i.e., of claim 49) having a molecular mass cut off of about 1000 kDa, and a first fluid stream having a pH of about 7.0.

Gritzner describes processes using membranes which are made of a "semipermeable, non-conducting material such as cellulose acetate membrane or the like used in dialysis", which are "colloid impermeable" and prevent "blood proteins from passing through the membranes" (col. 3, lines 49-55). Such membranes would therefore reasonably have mass cut-off values far lower than the 300 kDa cut-off of the selective membranes of claims 48-50.

Furthermore, Gritzner teaches that blood proteins are intended to permeate through a "[b]oundary membrane **10** [which] is [made] of a non-conducting material which is permeable to the substance to be separated" and "may be made of filter paper, filter cloth, ceramic filtering material or the like" (col. 3, lines 60-64). Such membranes would therefore reasonably have mass cut-off values far higher than the 300 kDa cut-off of the selective membranes of claims 48-50.

Gritzner states that the pH may be buffered to a "pH between the isoelectric points of the proteins to be separated" (col. 3, lines 11-14). In addition, the buffer used in Example 3 (which the Examiner cites for its disclosure of precipitated fibrinogen) has a pH of 6.35 (col.

8, line 55). Thus, the pH values taught by Gritzner are quite different from the pH 7.0 value of claims 48-50.

Thus, Gritzner also fails to describe the claimed isolation of fibrinogen from blood plasma by a method combining a first selective membrane having a molecular mass cut off of about 300 kDa, a second selective membrane (i.e., of claim 49) having a molecular mass cut off of about 1000 kDa, and a first fluid stream having a pH of about 7.0.

The sole example of Margolis describes an apparatus with a "stack of four membranes" each having a "molecular weight exclusion of approximately 50 kD" and a "buffered pH of 8.3" (col. 6, lines 35-47). Thus, both the molecular mass cut-off value and pH value taught by Margolis are quite different from those of claims 48-50 of the present application. Moreover, Margolis is silent in regard to the separation of blood clotting proteins from plasma.

Thus, Margolis also fails to describe the claimed isolation of fibrinogen from blood plasma by a method combining a first selective membrane having a molecular mass cut off of about 300 kDa, a second selective membrane (i.e., of claim 49) having a molecular mass cut off of about 1000 kDa, and a first fluid stream having a pH of about 7.0.

As discussed above, neither Laustsen, Gritzner, nor Margolis describe or suggest the processes of new claims 48-50 in which fibrinogen is isolated from blood plasma by a method combining a first selective membrane having a molecular mass cut-off of about 300 kDa, a second selective membrane (i.e., of claim 49) having a molecular mass cut-off of about 1000 kDa, and a first fluid stream having a pH of about 7.0. Thus, the combination of the applied references cannot reasonably teach or suggest the invention of claims 48-50.

As discussed in the specification (e.g., at page 1, lines 23-28, pages 14-16, Tables 3 and 4, and Figure 5), fibrinogen isolated by the claimed method has significantly different properties compared to fibrinogen isolated using precipitation methods. Since the difference in physical properties of fibrinogen isolated by the claimed method and those prepared by precipitation methods is likely due to differences in chemical composition (e.g., due to differences in the "essential related elements" isolated with the fibrinogen from blood plasma – *see* present specification at page 15, lines 20-28), it is reasonable that the fibrinogen of claim 51 is chemically different from fibrinogen provided by the combination of Laustsen,

Gritzner, and Margolis. Accordingly, the combined references cited by the Examiner fail to suggest the isolated fibrinogen of claim 51.

For the reasons stated above, Applicants respectfully submit that the present application is now in condition for allowance. Early notification thereof is earnestly solicited.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or to credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted,

Dated: 2/24/06

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